```
     FILE 'REGISTRY' ENTERED AT 10:35:37 ON 16 OCT 2008
L1              STRUCTURE UPLOADED
L2            0 S L1
L3            3 S L1 SSS FULL

     FILE 'HCAPLUS' ENTERED AT 10:36:13 ON 16 OCT 2008
L4           22 S L3
L5           11 S L4 AND (PY<2003 OR AY<2003 OR PRY<2003)

     FILE 'HCAPLUS' ENTERED AT 13:09:49 ON 16 OCT 2008
L1        77099 S (TNF(W)(ALPHA OR .ALPHA)) OR ((TUMOR NECROSIS FACTOR)(W)(ALPH
L2        77099 S (TNF(W)(ALPHA OR A)) OR ((TUMOR NECROSIS FACTOR)(W)(ALP
L3          173 S (REFLEX SYMPATHETIC SYSTROPHY) OR (COMPLEX REGIONAL PAIN SYND
L4           20 S L2 AND L3
L5            4 S L4 AND (PY<2003 OR AY<2003 OR PRY<2003)
```

=> file registry
COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION
FULL ESTIMATED COST | 0.21 | 0.21

FILE 'REGISTRY' ENTERED AT 10:35:37 ON 16 OCT 2008
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES: 15 OCT 2008 HIGHEST RN 1061881-29-5
DICTIONARY FILE UPDATES: 15 OCT 2008 HIGHEST RN 1061881-29-5

New CAS Information Use Policies, enter HELP USAGETERMS for details.

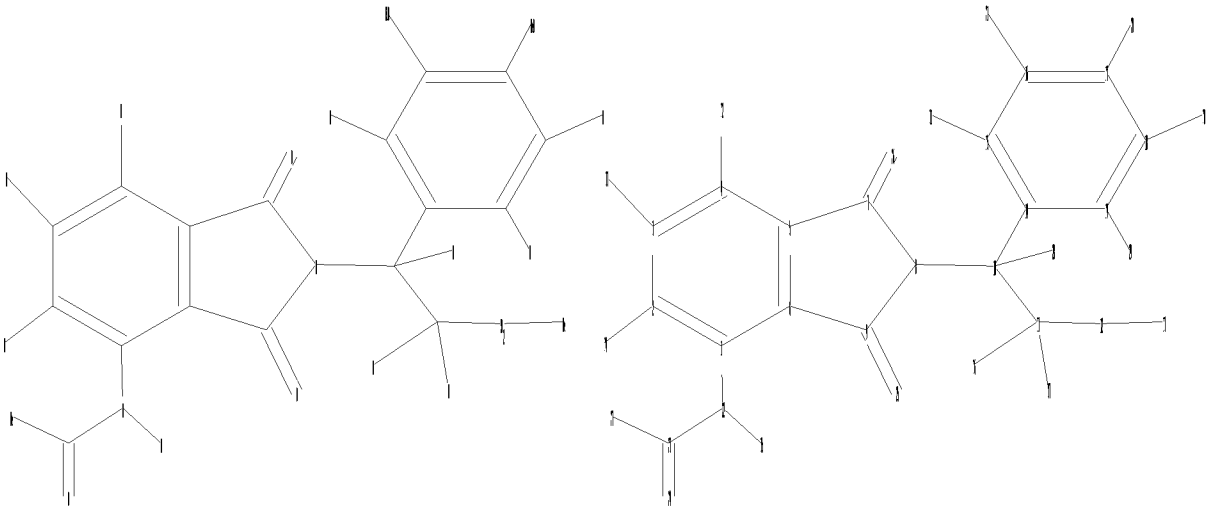
TSCA INFORMATION NOW CURRENT THROUGH July 5, 2008.

Please note that search-term pricing does apply when
conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document. For information
on property searching in REGISTRY, refer to:

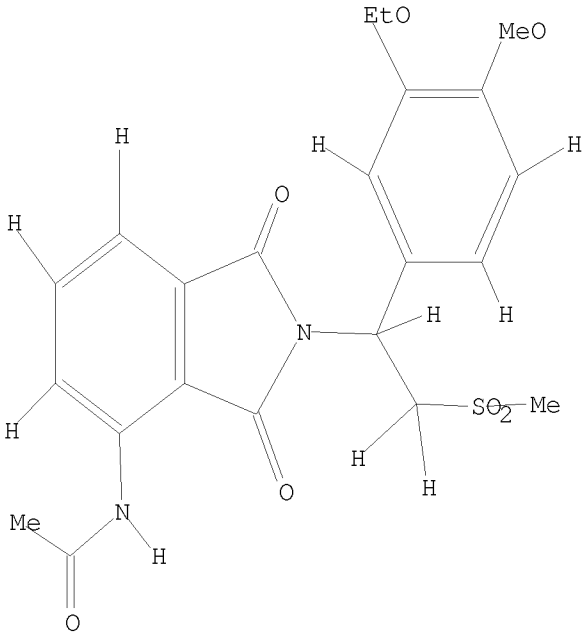
http://www.cas.org/support/stngen/stndoc/properties.html

=>
Uploading C:\Program Files\STNEXP\Queries\10693722specific.str



chain nodes :
10 11 12 13 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36
37
ring nodes :
1 2 3 4 5 6 7 8 9 14 15 16 17 18 19
chain bonds :
1-22 2-34 3-33 4-32 7-26 8-10 9-25 10-11 10-14 10-28 11-12 11-36 11-37
12-13 15-31 16-21 17-20 18-30 19-29 22-23 22-35 23-24 23-27
ring bonds :

```
1-2  1-6  2-3  3-4  4-5  5-6  5-7  6-9  7-8  8-9  14-15  14-19  15-16  16-17  17-18
18-19
exact/norm bonds :
1-22  5-7  6-9  7-8  7-26  8-9  8-10  9-25  22-23  23-24
exact bonds :
2-34  3-33  4-32  10-11  10-14  10-28  11-12  11-36  11-37  12-13  15-31  16-21
17-20  18-30  19-29  22-35  23-27
normalized bonds :
1-2  1-6  2-3  3-4  4-5  5-6  14-15  14-19  15-16  16-17  17-18  18-19


Match level :
1:Atom  2:Atom  3:Atom  4:Atom  5:Atom  6:Atom  7:Atom  8:Atom  9:Atom  10:CLASS
11:CLASS  12:CLASS  13:CLASS  14:Atom  15:Atom  16:Atom  17:Atom  18:Atom  19:Atom
20:CLASS  21:CLASS
22:CLASS  23:CLASS  24:CLASS  25:CLASS  26:CLASS  27:CLASS  28:CLASS  29:CLASS
30:CLASS  31:CLASS
32:CLASS  33:CLASS  34:CLASS  35:CLASS  36:CLASS  37:CLASS



L1      STRUCTURE UPLOADED

=> s l1
SAMPLE SEARCH INITIATED 10:35:59 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -        5 TO ITERATE

100.0% PROCESSED        5 ITERATIONS                                0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:             5 TO      234
PROJECTED ANSWERS:                0 TO        0

L2            0 SEA SSS SAM L1

=> d l1
L1 HAS NO ANSWERS
L1              STR
```



Structure attributes must be viewed using STN Express query preparation.

=> s l1 sss full
FULL SEARCH INITIATED 10:36:08 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 122 TO ITERATE

100.0% PROCESSED 122 ITERATIONS 3 ANSWERS
SEARCH TIME: 00.00.01

L3 3 SEA SSS FUL L1

=> file hcaplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	178.36	178.57

FILE 'HCAPLUS' ENTERED AT 10:36:13 ON 16 OCT 2008
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 16 Oct 2008 VOL 149 ISS 16
FILE LAST UPDATED: 15 Oct 2008 (20081015/ED)

HCAplus now includes complete International Patent Classification (IPC) reclassification data for the second quarter of 2008.

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

```
=> s l3
L4          22 L3

=> s l4 and (PY<2003 or AY<2003 or PRY<2003)
      22959050 PY<2003
       4498362 AY<2003
       3966940 PRY<2003
L5          11 L4 AND (PY<2003 OR AY<2003 OR PRY<2003)

=> d l5 1-11 ti abs bib

L5   ANSWER 1 OF 11  HCAPLUS  COPYRIGHT 2008 ACS on STN
TI   Solid forms of (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-
     4-acetylaminoisoindoline-1,3-dione, compositions thereof, and uses thereof
AB   Solid forms comprising (+)-2-[1-(3-Ethoxy-4-methoxyphenyl)-2-
     methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione (I), compns.
     comprising the solid forms, methods of making the solid forms and methods
     of their use are disclosed.  The methods include methods of treating
     and/or preventing disorders ameliorated by the reduction of levels of
     TNF-α or the inhibition of PDE4.  I was prepared by the reaction of
     1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethylamine with
     3-acetamidophthalic anhydride, yield = 59%.
AN   2008:1156159  HCAPLUS <<LOGINID::20081016>>
TI   Solid forms of (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-
     4-acetylaminoisoindoline-1,3-dione, compositions thereof, and uses thereof
IN   Muller, George W.; Schafer, Peter H.; Man, Hon-Wah; Ge, Chuansheng; Xu,
     Jean
PA   USA
SO   U.S. Pat. Appl. Publ., 66pp., Cont.-in-part of U.S. Ser. No. 106,142.
     CODEN: USXXCO
DT   Patent
LA   English
FAN.CNT 4
     PATENT NO.          KIND   DATE        APPLICATION NO.         DATE
     ---------------     ----   --------    --------------------    --------
PI   US 20080234359       A1    20080925    US 2008-79615           20080327 <--
     US 20030187052       A1    20031002    US 2003-392195          20030319 <--
     US 6962940           B2    20051108
     CN 1965823           A     20070523    CN 2006-10137407        20030320 <--
     US 20050192336       A1    20050901    US 2005-106142          20050413 <--
     US 7427638           B2    20080923
     US 20050267196       A1    20051201    US 2005-170308          20050628 <--
     US 7358272           B2    20080415
     US 20080027123       A1    20080131    US 2007-824523          20070629 <--
     US 20080207730       A1    20080828    US 2008-69282           20080208 <--
     US 20080242719       A1    20081002    US 2008-98379           20080404 <--
PRAI US 2002-366515P      P     20020320  <--
     US 2003-438450P      P     20030107
     US 2003-392195       A3    20030319
     US 2005-106142       A2    20050413
     CN 2003-811093       A3    20030320
     US 2005-170308       A3    20050628
```

L5 ANSWER 2 OF 11 HCAPLUS COPYRIGHT 2008 ACS on STN
TI Compositions comprising selective cytokine inhibitory drugs for treatment and management of macular degeneration and Methods of using thereof
AB Methods of treating, preventing and/or managing macular degeneration are disclosed. Specific embodiments encompass the administration of a selective cytokine inhibitory drug, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof, alone or in combination with a second active agent and/or surgery. Pharmaceutical compns., single unit dosage forms, and kits suitable for use in methods of the invention are also disclosed. Thus, patients with macular degeneration received conventional therapy with verteporfin and (+)-2-[1-(3-ethoxy-4 methoxyphenyl)-2-methylsulfonylethyl]-4 acetylaminoisoindoline 1,3-dione in an amount of about 20 mg/day as an adjuvant for 20 wk. The neovascular cascade was sufficiently hindered in those patients to indefinitely prolong the effects of the photodynamic therapy.
AN 2007:998162 HCAPLUS <<LOGINID::20081016>>
DN 147:330440
TI Compositions comprising selective cytokine inhibitory drugs for treatment and management of macular degeneration and Methods of using thereof
IN Zeldis, Jerome B.
PA USA
SO U.S. Pat. Appl. Publ., 30pp., Cont.-in-part of U.S. Ser. No. 699,110.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 20070207121	A1	20070906	US 2006-576140	20061215
	US 20040091454	A1	20040513	US 2003-699110	20031030 <--
	WO 2005044269	A1	20050519	WO 2004-US13253	20040428
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	AU 2008201418	A1	20080424	AU 2008-201418	20080327
PRAI	US 2003-699110	A2	20031030		
	WO 2004-US13253	W	20040428		
	US 2002-422900P	P	20021031	<--	
	AU 2003-285107	A3	20031031		

OS MARPAT 147:330440

L5 ANSWER 3 OF 11 HCAPLUS COPYRIGHT 2008 ACS on STN
TI Methods of the treatment or prevention of exercise-induced asthma using (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione
AB Methods of treating, managing or preventing exercise-induced asthma are disclosed. Specific methods encompass the administration of (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione alone or in combination with a second active agent. Pharmaceutical compns. and single unit dosage forms are also disclosed.

AN 2006:823362 HCAPLUS <<LOGINID::20081016>>
DN 145:224862
TI Methods of the treatment or prevention of exercise-induced asthma using (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione
IN Muller, George W.; Schafer, Peter H.; Rohane, Patricia E. W.
PA Celgene Corporation, USA
SO U.S. Pat. Appl. Publ., 32pp., Cont.-in-part of U.S. Ser. No. 106,142.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	US 20060183788	A1	20060817	US 2006-392846	20060328	<--
	US 7276529	B2	20071002			
	US 20030187052	A1	20031002	US 2003-392195	20030319	<--
	US 6962940	B2	20051108			
	CN 1965823	A	20070523	CN 2006-10137407	20030320	<--
	US 20050192336	A1	20050901	US 2005-106142	20050413	<--
	US 7427638	B2	20080923			
	US 20050267196	A1	20051201	US 2005-170308	20050628	<--
	US 7358272	B2	20080415			
	US 20080027123	A1	20080131	US 2007-824523	20070629	<--
	US 20080207730	A1	20080828	US 2008-69282	20080208	<--
	US 20080242719	A1	20081002	US 2008-98379	20080404	<--
PRAI	US 2002-366515P	P	20020320	<--		
	US 2003-438450P	P	20030107			
	US 2003-392195	A3	20030319			
	US 2005-106142	A2	20050413			
	CN 2003-811093	A3	20030320			
	US 2005-170308	A3	20050628			

RE.CNT 131 THERE ARE 131 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

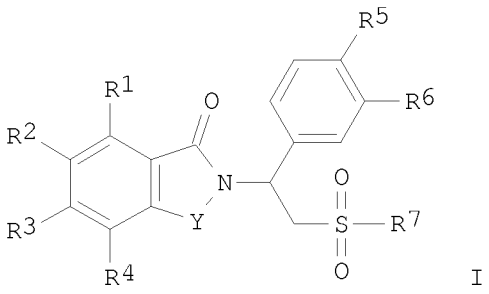
L5 ANSWER 4 OF 11 HCAPLUS COPYRIGHT 2008 ACS on STN
TI Methods of the treatment of psoriatic arthritis using (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione
AB Methods of treating, managing or preventing psoriatic arthritis are disclosed. Specific methods encompass the administration of (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione alone or in combination with a second active agent. Pharmaceutical compns. and single unit dosage forms are also disclosed.
AN 2006:821184 HCAPLUS <<LOGINID::20081016>>
DN 145:224861
TI Methods of the treatment of psoriatic arthritis using (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione
IN Muller, George W.; Schafer, Peter H.; Rohane, Patricia E. W.
PA Celgene Corporation, USA
SO U.S. Pat. Appl. Publ., 19pp., Cont.-in-part of U.S. Ser. No. 106,142.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	US 20060183787	A1	20060817	US 2006-392845	20060328	<--
	US 7208516	B2	20070424			

	US 20030187052	A1	20031002	US 2003-392195	20030319 <--
	US 6962940	B2	20051108		
	CN 1965823	A	20070523	CN 2006-10137407	20030320 <--
	US 20050192336	A1	20050901	US 2005-106142	20050413 <--
	US 7427638	B2	20080923		
	US 20050267196	A1	20051201	US 2005-170308	20050628 <--
	US 7358272	B2	20080415		
	US 20080027123	A1	20080131	US 2007-824523	20070629 <--
	US 20080207730	A1	20080828	US 2008-69282	20080208 <--
	US 20080242719	A1	20081002	US 2008-98379	20080404 <--
PRAI	US 2002-366515P	P	20020320 <--		
	US 2003-438450P	P	20030107		
	US 2003-392195	A3	20030319		
	US 2005-106142	A2	20050413		
	CN 2003-811093	A3	20030320		
	US 2005-170308	A3	20050628		

RE.CNT 130 THERE ARE 130 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 5 OF 11 HCAPLUS COPYRIGHT 2008 ACS on STN
TI Preparation of substituted phenethyl sulfones and methods of reducing TNFα levels
GI



I

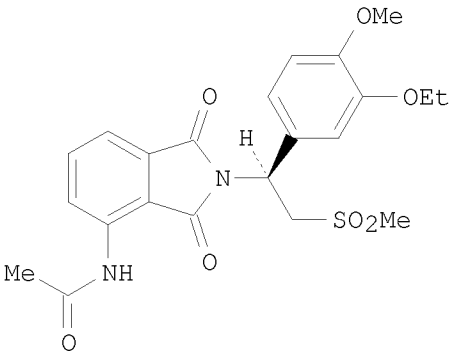
AB The title compds. I [Y = CO, CH2, SO2, CH2C(O); R1-R4 = H, halo, alkyl, alkoxy, etc.; R5, R6 = H, alkyl, alkoxy, CN, etc.; R7 = OH, alkyl, Ph, etc.], useful for reducing TNFα levels and treating inflammatory and autoimmune diseases, were prepared and formulated. E.g., a 2-step synthesis of 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]isoindolin-1-one, starting from di-Me sulfone and 3-ethoxy-4-methoxybenzaldehyde, was given.
AN 2006:425851 HCAPLUS <<LOGINID::20081016>>
DN 147:189068
TI Preparation of substituted phenethyl sulfones and methods of reducing TNFα levels
IN Man, Hon-Wah; Muller, George W.
PA Celgene Corporation, USA
SO Aust. Pat. Appl., 53 pp.
CODEN: AUXXCM
DT Patent
LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	AU 2006200033	A1	20060202	AU 2006-200033	20060106
	AU 2006200033	B2	20080814		
	AU 2003203681	A1	20030703	AU 2003-203681	20030409 <--

```
     AU 2003203681         B2    20051006
PRAI AU 2003-203681        A3    20030409
     AU 2000-14472         A3    19991019  <--
     WO 1999-US24376       W     19991019  <--
OS   CASREACT 147:189068

L5   ANSWER 6 OF 11  HCAPLUS  COPYRIGHT 2008 ACS on STN
TI   Methods of using and compositions comprising selective cytokine inhibitory
     drugs for treatment and management of macular degeneration
AB   Methods of treating, preventing and/or managing macular degeneration are
     disclosed.  Specific embodiments encompass the administration of a
     selective cytokine inhibitory drug, or a pharmaceutically acceptable salt,
     solvate, hydrate, stereoisomer, clathrate, or prodrug thereof, alone or in
     combination with a second active agent and/or surgery.  Pharmaceutical
     compns., single unit dosage forms, and kits suitable for use in methods of
     the invention are also disclosed.  Patients with macular degeneration were
     treated by photodynamic therapy with verteporfin alone, or with the addition
     of 20 mg/day of selective cytokine inhibitory drug (+)-2-[1-(3-ethoxy-4
     methoxyphenyl)-2-methylsulfonylethyl]-4 acetylaminoisoindoline 1,3-dione.
     The neovascular cascade is sufficiently hindered in the group receiving
     (+)-2-[1-(3-ethoxy-4 methoxyphenyl)-2-methylsulfonylethyl]-4
     acetylaminoisoindoline 1,3-dione to indefinitely prolong the effects of
     the photodynamic therapy.
AN   2004:392056  HCAPLUS <<LOGINID::20081016>>
DN   140:386062
TI   Methods of using and compositions comprising selective cytokine inhibitory
     drugs for treatment and management of macular degeneration
IN   Zeldis, Jerome B.
PA   USA
SO   U.S. Pat. Appl. Publ., 19 pp.
     CODEN: USXXCO
DT   Patent
LA   English
FAN.CNT 2
     PATENT NO.          KIND   DATE        APPLICATION NO.         DATE
     ---------------     ----   --------    --------------------    --------
PI   US 20040091454       A1    20040513    US 2003-699110          20031030 <--
     CA 2504263           A1    20040521    CA 2003-2504263         20031031 <--
     WO 2004041181        A2    20040521    WO 2003-US34535         20031031 <--
     WO 2004041181        A3    20050217
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE,
             GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK,
             LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ,
             OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,
             TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,
             BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE,
             ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK,
             TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
     AU 2003285107        A1    20040607    AU 2003-285107          20031031 <--
     AU 2003285107        B2    20080110
     EP 1567148           A2    20050831    EP 2003-779423          20031031 <--
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
     BR 2003015889        A     20051004    BR 2003-15889           20031031 <--
     CN 1731997           A     20060208    CN 2003-80108090        20031031 <--
     JP 2006509743        T     20060323    JP 2004-550274          20031031 <--
     NZ 540185            A     20080131    NZ 2003-540185          20031031 <--
     AU 2004286824        A1    20050519    AU 2004-286824          20040428
     CA 2543618           A1    20050519    CA 2004-2543618         20040428
```

WO 2005044269 A1 20050519 WO 2004-US13253 20040428
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
EP 1684756 A1 20060802 EP 2004-750923 20040428
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR
BR 2004015970 A 20070123 BR 2004-15970 20040428
CN 1901909 A 20070124 CN 2004-80039431 20040428
JP 2007509932 T 20070419 JP 2006-537956 20040428
MX 2005PA04486 A 20050726 MX 2005-PA4486 20050427 <--
MX 2006PA04622 A 20060720 MX 2006-PA4622 20060426
US 20070207121 A1 20070906 US 2006-576140 20061215
AU 2008201418 A1 20080424 AU 2008-201418 20080327
PRAI US 2002-422900P P 20021031 <--
US 2003-699110 A 20031030
AU 2003-285107 A3 20031031
WO 2003-US34535 W 20031031
WO 2004-US13253 W 20040428
OS MARPAT 140:386062

L5 ANSWER 7 OF 11 HCAPLUS COPYRIGHT 2008 ACS on STN
TI Use of (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione and compositions thereof for inhibiting TNF-α production and PDE4 activity
GI



I

AB The invention discloses stereomerically pure (S)-2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione (+)-I, substantially free of its (-)-isomer, and prodrugs, metabolites, polymorphs, salts, solvates, hydrates, and clathrates thereof. Methods of using and pharmaceutical compns. comprising (+)-I for treating and/or preventing disorders ameliorated by the reduction of levels of tumor necrosis factor α (TNF-α) or the inhibition of phosphodiesterase IV (PDE4) are also disclosed. Examples include the synthesis and resolution of (+)-I, thirteen

bioassays, an aqueous solubility study, and three formulations. For instance, 3-nitrophthalic acid was hydrogenated using 10% Pd/C in EtOH to give the amine (84%), which was condensed with Ac2O to afford 3-acetamidophthalic anhydride (61%). Reaction of the phthalic anhydride with 1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethylamine to give I (59%), followed by resolution with N-acetyl-L-leucine in MeOH provided (+)-I (90% recovery, 98.4% ee). The latter inhibited LPS-induced TNF-α production by human whole blood and PDE4 activity with IC50 values of 294 nM and 73.5 nM, resp. (+)-I showed >500-fold to >40,000-fold selectivity for PDE4 over PDE1, PDE2, PDE3, PDE5, and PDE6. In addition, (+)-I suppressed LPS-induced lung neutrophilia in conscious ferrets with an ED50 of 0.8 mg/kg. Thus, (+)-I and its pharmaceutical compns. are useful for treating and/or preventing cancer, depression, and a variety of allergic, inflammatory, and autoimmune disorders (no data).

AN 2003:777583 HCAPLUS <<LOGINID::20081016>>

DN 139:296870

TI Use of (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione and compositions thereof for inhibiting TNF-α production and PDE4 activity

IN Schafer, Peter H.; Muller, George W.; Man, Hon-Wah; Ge, Chuansheng

PA Celgene Corporation, USA

SO PCT Int. Appl., 57 pp.
CODEN: PIXXD2

DT Patent

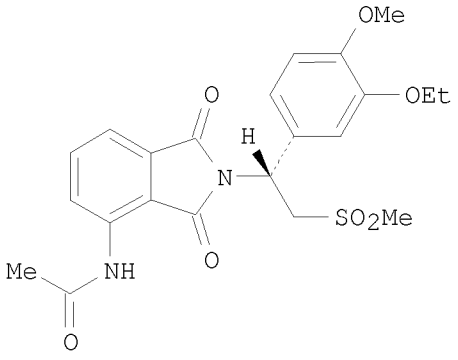
LA English

FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003080049	A1	20031002	WO 2003-US8738	20030320 <--
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	CA 2479666	A1	20031002	CA 2003-2479666	20030320 <--
	AU 2003224729	A1	20031008	AU 2003-224729	20030320 <--
	AU 2003224729	B2	20080103		
	EP 1485087	A1	20041215	EP 2003-721414	20030320 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
	CN 1652772	A	20050810	CN 2003-811093	20030320 <--
	JP 2005525386	T	20050825	JP 2003-577877	20030320 <--
	NZ 535798	A	20060428	NZ 2003-535798	20030320 <--
	CN 1965823	A	20070523	CN 2006-10137407	20030320 <--
	MX 2004PA09075	A	20050713	MX 2004-PA9075	20040920 <--
	US 20080027123	A1	20080131	US 2007-824523	20070629 <--
	US 20080207730	A1	20080828	US 2008-69282	20080208 <--
	US 20080242719	A1	20081002	US 2008-98379	20080404 <--
PRAI	US 2002-366515P	P	20020320	<--	
	US 2003-438450P	P	20030107		
	US 2003-392195	A3	20030319		
	CN 2003-811093	A3	20030320		
	WO 2003-US8738	W	20030320		
	US 2005-170308	A3	20050628		

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 8 OF 11 HCAPLUS COPYRIGHT 2008 ACS on STN
TI Use of (-)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione and compositions thereof for inhibiting TNF-α production and PDE4 activity
GI

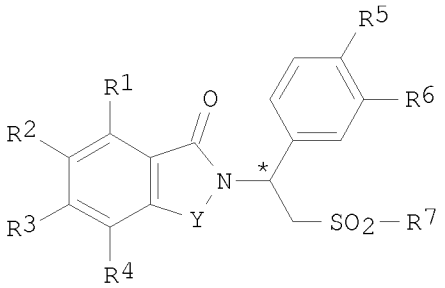


I

AB The invention discloses stereomerically pure (R)-2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione (-)-I, substantially free of its (+)-isomer, and prodrugs, metabolites, polymorphs, salts, solvates, hydrates, and clathrates thereof. Methods of using and pharmaceutical compns. comprising (-)-I for treating and/or preventing disorders ameliorated by the reduction of levels of tumor necrosis factor α (TNF-α) or the inhibition of phosphodiesterase IV (PDE4) are also disclosed. Examples include the synthesis and resolution of (-)-I, seven bioassays, an aqueous solubility study, and three formulations. For instance, 3-nitrophthalic acid was hydrogenated using 10% Pd/C in EtOH to give the amine (84%), which was condensed with Ac2O to afford 3-acetamidophthalic anhydride (61%). Reaction of the phthalic anhydride with 1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethylamine to give I (59%), followed by resolution with N-acetyl-D-leucine in MeOH provided (-)-I (90% recovery, 98.4% ee). The latter inhibited LPS-induced TNF-α production by human whole blood and PDE4 activity with IC50 values of 371 nM and 611 nM, resp. (-)-I showed >45-fold to >39,000-fold selectivity for PDE4 over PDE1, PDE2, PDE3, PDE5, and PDE6. Thus, (-)-I and its pharmaceutical compns. are useful for treating and/or preventing cancer, depression, and a variety of allergic, inflammatory, and autoimmune disorders (no data).
AN 2003:777582 HCAPLUS <<LOGINID::20081016>>
DN 139:296869
TI Use of (-)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione and compositions thereof for inhibiting TNF-α production and PDE4 activity
IN Schafer, Peter H.; Muller, George W.; Man, Hon-Wah; Ge, Chuansheng
PA Celgene Corporation, USA
SO PCT Int. Appl., 49 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

```
     ---------------     ----   --------    --------------------   --------
PI   WO 2003080048        A1    20031002    WO 2003-US8737         20030320 <--
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
             PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ,
             UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
             KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
             FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
             BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
     AU 2003222034         A1    20031008    AU 2003-222034         20030320 <--
PRAI US 2002-366516P       P     20020320  <--
     US 2003-438448P       P     20030107
     WO 2003-US8737        W     20030320
RE.CNT  3     THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
              ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5   ANSWER 9 OF 11  HCAPLUS  COPYRIGHT 2008 ACS on STN
TI   Interactions between myeloma and endothelial cells and the effects of
     thalidomide and its analogues
AB   Modeling the situation observed in vivo, the authors examined the effects of
     thalidomide and its analogs in co-cultures of myeloma and endothelial
     cells.  It was found that myeloma cells in co-culture had significantly
     lower levels of CC-10004- and CC-1088-induced apoptosis than those
     cultured alone.  Interestingly, basal apoptosis was also lower in
     RPMI-8226/S co-cultured with endothelial cells compared to myeloma cell
     culture.  The authors' data suggest that myeloma/endothelial cell
     interactions in co-culture have a significant protective effect on both
     basal and drug-induced levels of apoptosis in myeloma cells.
AN   2003:649755  HCAPLUS <<LOGINID::20081016>>
DN   140:228565
TI   Interactions between myeloma and endothelial cells and the effects of
     thalidomide and its analogues
AU   Molostvov, G.; Morris, A.; Rose, P.; Basu, S.
CS   University of Warwick, Coventry, UK
SO   Free Papers - Annual Meeting of the European Haematology Association, 7th,
     Florence, Italy, June 6-9, 2002 (2002), 263-266 Publisher:
     Monduzzi Editore, Bologna, Italy.
     CODEN: 69EIOR; ISBN: 88-323-2606-X
DT   Conference
LA   English
RE.CNT  3     THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
              ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5   ANSWER 10 OF 11  HCAPLUS  COPYRIGHT 2008 ACS on STN
TI   Preparation of substituted phenethylsulfones for reducing TNFα
     levels
GI
```



I

AB The title compds. [I; the carbon atom designated "*" constitutes a center of chirality; Y = CO, CH2< CH2CO; R1-R4 = H, halo, alkyl, etc.; R5, R6 = H, alkyl, alkoxy, etc.; R7 = OH, alkyl, Ph, etc.] which reduce the levels of TNFα and inhibit PDE IV in a mammal (no data), were prepared and formulated. Typical embodiments are 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-aminoisoindoline-1,3-dione and 2-[1-(3-cyclopentyloxy-4-methoxyphenyl)-2-methylsulfonylethyl]isoindoline-1,3-dione.

AN 2000:78904 HCAPLUS <<LOGINID::20081016>>

DN 132:107873

TI Preparation of substituted phenethylsulfones for reducing TNFα levels

IN Muller, George W.; Man, Hon-wah

PA Celgene Corporation, USA

SO U.S., 13 pp.
CODEN: USXXAM

DT Patent

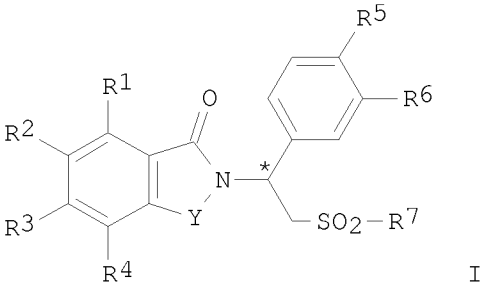
LA English

FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6020358	A	20000201	US 1998-183049	19981030 <--
	US 6011050	A	20000104	US 1999-340617	19990629 <--
	CA 2348993	A1	20000511	CA 1999-2348993	19991019 <--
	WO 2000025777	A1	20000511	WO 1999-US24376	19991019 <--
	W: AU, BR, CA, IL, IS, JP, LU, NO, NZ, PT, RU, SE, SG, ZA, AM, AZ, BY, KG, KZ, MD, TJ, TM				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	EP 1126839	A1	20010829	EP 1999-971317	19991019 <--
	EP 1126839	B1	20070103		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY				
	BR 9915201	A	20011030	BR 1999-15201	19991019 <--
	JP 2002528496	T	20020903	JP 2000-579218	19991019 <--
	AU 756308	B2	20030109	AU 2000-14472	19991019 <--
	NZ 511253	A	20030228	NZ 1999-511253	19991019 <--
	AT 350033	T	20070115	AT 1999-971317	19991019 <--
	EP 1752148	A2	20070214	EP 2006-23050	19991019 <--
	EP 1752148	A3	20070314		
	R: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	ES 2278467	T3	20070801	ES 1999-971317	19991019 <--
	NO 2001002021	A	20010626	NO 2001-2021	20010424 <--
	NO 319790	B1	20050912		
	HK 1038696	A1	20070803	HK 2002-100185	20020110 <--
PRAI	US 1998-183049	A3	19981030 <--		

EP 1999-971317 A3 19991019 <--
WO 1999-US24376 W 19991019 <--
OS MARPAT 132:107873
RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 11 OF 11 HCAPLUS COPYRIGHT 2008 ACS on STN
TI Preparation of substituted phenethylsulfones and method of reducing TNFα levels
GI



I

AB The title compds. [I; the carbon atom designated * constitutes a center of chirality; Y = SO2, CO, CH2; R1-R4 = H, halo, alkyl, etc.; R5, R6 = H, alkyl, alkoxy, etc.; R7 = OH, alkyl, Ph, etc.], useful in reducing the levels of TNFα and inhibiting PDE IV (no data), were prepared and formulated. Typical embodiments are 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-aminoisoindoline-1,3-dione and 2-[1-(3-cyclopentyloxy-4-methoxyphenyl)-2-methylsulfonylethyl]isoindoline-1,3-dione (prepns. were given).
AN 2000:10631 HCAPLUS <<LOGINID::20081016>>
DN 132:64167
TI Preparation of substituted phenethylsulfones and method of reducing TNFα levels
IN Muller, George W.; Man, Hon-Wah
PA Celgene Corporation, USA
SO U.S., 12 pp., Division of U.S. Ser. No. 183,049.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 3

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6011050	A	20000104	US 1999-340617	19990629 <--
US 6020358	A	20000201	US 1998-183049	19981030 <--

PRAI US 1998-183049 A3 19981030 <--
OS MARPAT 132:64167
RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> file hcaplus
COST IN U.S. DOLLARS

	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'HCAPLUS' ENTERED AT 13:09:49 ON 16 OCT 2008
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.

PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 16 Oct 2008 VOL 149 ISS 16
FILE LAST UPDATED: 15 Oct 2008 (20081015/ED)

HCAplus now includes complete International Patent Classification (IPC)
reclassification data for the second quarter of 2008.

New CAS Information Use Policies, enter HELP USAGETERMS for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> s (TNF(alpha or .alpha)) or ((tumor necrosis factor)(w)(alpha or α))
MISSING OPERATOR 'TNF(ALPHA'
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> s (TNF(w)(alpha or .alpha)) or ((tumor necrosis factor)(w)(alpha or α))
         79781 TNF
       1800010 ALPHA
       1800010 .ALPHA
                 (ALPHA)
         60832 TNF(W)(ALPHA OR .ALPHA)
        470274 TUMOR
        146202 NECROSIS
       1160676 FACTOR
         78189 TUMOR NECROSIS FACTOR
                 (TUMOR(W)NECROSIS(W)FACTOR)
       1800010 ALPHA
       1800010 A
                 (ALPHA)
         47757 (TUMOR NECROSIS FACTOR)(W)(ALPHA OR A)
L1   77099 (TNF(W)(ALPHA OR .ALPHA)) OR ((TUMOR NECROSIS FACTOR)(W)(ALPHA
               OR A))

=> s (TNF(w)(alpha or α)) or ((tumor necrosis factor)(w)(alpha or α))
         79781 TNF
       1800010 ALPHA
       1800010 A
                 (ALPHA)
         60832 TNF(W)(ALPHA OR A)
        470274 TUMOR
        146202 NECROSIS
       1160676 FACTOR
         78189 TUMOR NECROSIS FACTOR
                 (TUMOR(W)NECROSIS(W)FACTOR)
       1800010 ALPHA
       1800010 A

```
                (ALPHA)
         47757 (TUMOR NECROSIS FACTOR)(W)(ALPHA OR A)
L2       77099 (TNF(W)(ALPHA OR A)) OR ((TUMOR NECROSIS FACTOR)(W)(ALPHA
               OR A))

=> s (reflex sympathetic systrophy) or (complex regional pain syndrome)
         26744 REFLEX
         41727 SYMPATHETIC
             2 SYSTROPHY
             0 REFLEX SYMPATHETIC SYSTROPHY
               (REFLEX(W)SYMPATHETIC(W)SYSTROPHY)
       1440681 COMPLEX
         74307 REGIONAL
         63422 PAIN
        149117 SYNDROME
           173 COMPLEX REGIONAL PAIN SYNDROME
               (COMPLEX(W)REGIONAL(W)PAIN(W)SYNDROME)
L3         173 (REFLEX SYMPATHETIC SYSTROPHY) OR (COMPLEX REGIONAL PAIN SYNDROM
               E)

=> s l2 and l3
L4          20 L2 AND L3

=> s l4 and (PY<2003 or AY<2003 or PRY<2003)
      22959050 PY<2003
       4498362 AY<2003
       3966940 PRY<2003
L5           4 L4 AND (PY<2003 OR AY<2003 OR PRY<2003)

=> d l5 1-4 ti abs bib

L5   ANSWER 1 OF 4  HCAPLUS  COPYRIGHT 2008 ACS on STN
TI   Methods of using and compositions comprising selective cytokine inhibitory
     drug for treatment, modification and management of pain
AB   Methods of treating, preventing, modifying and managing various types of
     pain are disclosed.  Specific methods comprise the administration of a
     selective cytokine inhibitory drug, or a pharmaceutically acceptable salt,
     solvate, hydrate, stereoisomer, clathrate, or prodrug thereof, alone or in
     combination with a second active agent and/or surgery, psychol. or phys.
     therapy.  Pharmaceutical compns., single unit dosage forms, and kits
     suitable for use in methods of the invention are also disclosed.
AN   2005:426388  HCAPLUS <<LOGINID::20081016>>
DN   142:457121
TI   Methods of using and compositions comprising selective cytokine inhibitory
     drug for treatment, modification and management of pain
IN   Zeldis, Jerome B.; Faleck, Herbert; Manning, Donald C.
PA   Celgene Corporation, USA
SO   PCT Int. Appl., 85 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 6
     PATENT NO.          KIND   DATE        APPLICATION NO.        DATE
     ---------------     ----   --------    --------------------   --------
PI   WO 2005043971        A2    20050519    WO 2004-US12722        20040423
     WO 2005043971        A3    20050714
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
             NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
```

TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

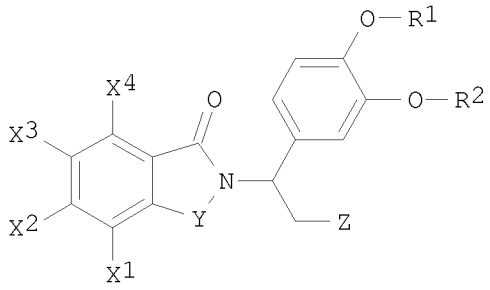
US	20050203142	A1	20050915	US 2003-693794	20031023 <--
AU	2004286819	A1	20050519	AU 2004-286819	20040423
CA	2543132	A1	20050519	CA 2004-2543132	20040423
EP	1679967	A2	20060719	EP 2004-750613	20040423
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR				
BR	2004015649	A	20061219	BR 2004-15649	20040423
CN	1897816	A	20070117	CN 2004-80038252	20040423
JP	2007524656	T	20070830	JP 2006-536543	20040423
MX	2006PA04381	A	20060706	MX 2006-PA4381	20060420
US	20070161696	A1	20070712	US 2007-576139	20070102
PRAI US	2003-693794	A	20031023		
US	2002-421003P	P	20021024 <--		
US	2003-693722	A	20031023		
WO	2004-US12722	W	20040423		

OS MARPAT 142:457121

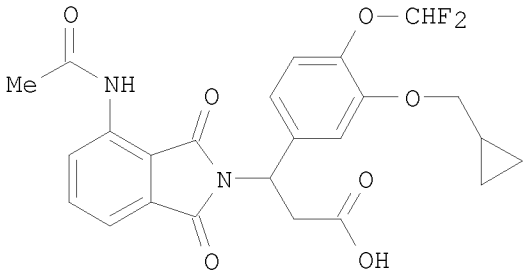
L5 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2008 ACS on STN

TI Preparation of 2-(fluoroalkoxyphenylalkyl)-1,3-dihydroisoindolones as PDE4, TNF-α , and/or MMP inhibitors

GI



I



II

AB Title compds. I [wherein X1-X4 = independently H, halo, NO2, NH2, CF3, alkyl, cycloalkyl(alkyl), NR7R8-(alkyl), R8CONH-(alkyl), NR7R8CONH-(alkyl), R8OCONH-(alkyl), R8O-(alkyl), imidazolyl(alkyl), pyrrolyl(alkyl), oxadiazolyl(alkyl), triazolyl(alkyl); or X1 and X2 or X2 and X3 or X3 and X4 may be taken together to form a (hetero)cycloalkyl ring; Y = CO, CH2, CH2CO, COCH2, SO2; Z = H, COR3, alkylsulfonyl(alkyl),

alkyl, CH2OH, alkoxymethyl, CN; R1 and R2 = independently CHF2, alkyl, cycloalkyl(alkyl); at least one of R1 and R2 = CHF2; R3 = NR4R5, alkyl, OH, alkoxy, (un)substituted Ph, PhCH2; R4 and R5 = independently H, alkyl, OH, OCOR6; R6 = alkyl(amino), Ph, PhCH2, aryl; R7 and R8 = independently H, alkyl, cycloalkyl(alkyl), NR7R8-alkyl, R8O-alkyl, Ph, PhCH2, aryl; or pharmaceutically acceptable salts, hydrates, solvates, clathrates, stereoisomers, and prodrugs thereof] were prepared For example, alkylation of 3,4-dihydroxybenzaldehyde with chlorodifluoromethane in the presence of K2CO3 in DMF gave 4-difluoromethoxy-3-hydroxybenzaldehyde (15%), which was further alkylated with bromomethylcyclopropane under the same conditions to afford 3-cyclopropylmethoxy-4-difluoromethoxybenzaldehyde (100%). Reaction of the benzaldehyde with ammonium acetate in 95% EtOH, followed by addition of malonic acid provided 3-amino-3-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)propionic acid (52%). Condensation of the amine with 3-acetamidophthalic anhydride using sodium acetate in AcOH yielded the isoindoledione II (85%). I and their pharmaceutical compns., optionally in combination with another therapeutic agent, are useful for the treatment or prevention of diseases associated with phosphodiesterase 4 (PDE4) inhibition, abnormal tumor necrosis factor α (TNF-α) levels , and/or matrix metalloproteinase (MMP) inhibition, such as myelodysplastic syndrome, myeloproliferative disease, complex regional pain syndrome, cancer, inflammatory diseases, and autoimmune diseases (no data).

AN 2004:589381 HCAPLUS <<LOGINID::20081016>>
DN 141:140314

TI Preparation of 2-(fluoroalkoxyphenylalkyl)-1,3-dihydroisoindolones as PDE4, TNF-α , and/or MMP inhibitors

IN Muller, George W.; Man, Hon-Wah; Zhang, Weihong
PA Celgene Corporation, USA

SO PCT Int. Appl., 98 pp.
CODEN: PIXXD2
DT Patent
LA English

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004060313	A2	20040722	WO 2003-US41568	20031229 <--
WO 2004060313	A3	20050915		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2511843	A1	20040722	CA 2003-2511843	20031229 <--
AU 2003303511	A1	20040729	AU 2003-303511	20031229 <--
US 20040204448	A1	20041014	US 2003-748085	20031229 <--
US 7173058	B2	20070206		
EP 1587474	A2	20051026	EP 2003-808605	20031229 <--
EP 1587474	A3	20051102		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2003017885	A	20051206	BR 2003-17885	20031229 <--
JP 2006515310	T	20060525	JP 2004-565816	20031229 <--
CN 1802353	A	20060712	CN 2003-80109907	20031229 <--
MX 2005PA06998	A	20050818	MX 2005-PA6998	20050627 <--

```
     US 20070072902       A1    20070329    US 2006-601355         20061116 <--
PRAI US 2002-436975P      P     20021230  <--
     US 2003-748085       A3    20031229
     WO 2003-US41568      W     20031229
OS   MARPAT 141:140314

L5   ANSWER 3 OF 4  HCAPLUS  COPYRIGHT 2008 ACS on STN
TI   Evidence for local inflammation in complex regional
     pain syndrome type 1
AB   BACKGROUND: The pathophysiol. of complex regional
     pain syndrome type 1 (CRPS 1) is still a matter of
     debate.  Peripheral afferent, efferent and central mechanisms are
     supposed.  Based on clin. signs and symptoms (e.g. edema, local temperature
     changes and chronic pain) local inflammation is suspected.  Aim: To determine
     the involvement of neuropetides, cytokines and eicosanoids as locally
     formed mediators of inflammation.  Methods: In this study, nine patients
     with proven CRPS 1 were included.  Disease activity and impairment was
     determined by means of a Visual Analog Scale, the McGill Pain Questionnaire,
     the difference in volume and temperature between involved and uninvolved
     extremities, and the reduction in active range of motion of the involved
     extremity.  Venous blood was sampled from and suction blisters made on the
     involved and uninvolved extremities for measurement of cytokines
     interleukin (IL)-6, IL-1β and  tumor necrosis
     factor-α  (TNF-α ), the
     neuropetides NPY and CRGP, and prostaglandin E2.  Results: The patients
     included in this study did have a moderate to serious disease activity and
     impairment.  In plasma, no changes of mediators of inflammation were observed
     In blister fluid, however, significantly higher levels of IL-6 and
     TNF-α  in the involved extremity were observed in
     comparison with the uninvolved extremity.  Conclusions: This is the first
     time that involvement of mediators of inflammation in CRPS 1 has been so
     clearly and directly demonstrated.  This observation opens new approaches
     for the successful use and development of immunosuppressives in CRPS 1.
AN   2002:305303  HCAPLUS <<LOGINID::20081016>>
DN   137:167971
TI   Evidence for local inflammation in complex regional
     pain syndrome type 1
AU   Huygen, Frank J. P. M.; De Bruijn, Anke G. J.; De Bruin, Martha T.;
     Groeneweg, J. George; Klein, Jan; Zijlstra, Freek J.
CS   Pain Treatment Centre, Erasmus Medical Centre, Rotterdam, 3000 CA, Neth.
SO   Mediators of Inflammation (2002), 11(1), 47-51
     CODEN: MNFLEF; ISSN: 0962-9351
PB   Taylor & Francis Ltd.
DT   Journal
LA   English
RE.CNT  32    THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD
              ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5   ANSWER 4 OF 4  HCAPLUS  COPYRIGHT 2008 ACS on STN
TI   Increased production of nitric oxide stimulated by interferon-γ from
     peripheral blood monocytes in patients with complex
     regional pain syndrome
AB   This study examines immediate nitric oxide (NO) release from monocytes
     following interleukin-1β (IL-1β), interferon-γ
     (IFN-γ), and  tumor necrosis factor-.
     alpha. (TNF-α ) challenge in patients
     with complex regional pain syndrome
     (CRPS).  Study patients exhibited the following: (1), mech. allodynia;
     (2), evidence of either vasomotor or sudomotor disturbance; and (3),
     concordant painful allodynia documented with quant. sensory testing that
     was temporarily abolished with sympathetic block.  Ten subjects (CRPS,
```

N=5; control, N=5) were enrolled. Peripheral blood monocytes were challenged with 100 μL of IL-1β (1 ng), IFN-γ (1 ng), TNF-α (0.01 ng), and normal saline (NS) and the resultant immediate NO release measured. Subjects with CRPS exhibited a statistically significant increase in NO release in response to IFN-γ compared with controls. The NO responses to IFN-γ in excess of NS and as the ratio IFN-γ/NS were also significantly increased.

AN 2002:212993 HCAPLUS <<LOGINID::20081016>>
DN 136:368210
TI Increased production of nitric oxide stimulated by interferon-γ from peripheral blood monocytes in patients with complex regional pain syndrome
AU Hartrick, Craig T.
CS Department of Anesthesiology and Perioperative Medicine, William Beaumont Hospital, Royal Oak, MI, 48073, USA
SO Neuroscience Letters (2002), 323(1), 75-77
CODEN: NELED5; ISSN: 0304-3940
PB Elsevier Science Ireland Ltd.
DT Journal
LA English
RE.CNT 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT